REMARKS

The Examiner is thanked for the due consideration given the application. The specification has been amended to add generic language to trade names.

Claims 19-25, 27-34 and 36-42 are pending in the application. Claims 26 and 35 have been canceled and their subject matter has been generally incorporated into independent claims 19 and 33, respectively. Claims 19 and 33 have been further amended to improve their language. Claims 20, 21, 30, 32 and 39 have been amended to improve their language in a non-narrowing fashion. Claim 42 is new and generally sets forth subject matter found in claims 19 and 26-29.

No new matter is believed to be added to the application by this amendment.

Rejection Under 35 USC §112, First Paragraph

Claims 30, 32, 39 and 41 have been rejected under 35 USC §112, first paragraph as failing to comply with the written description requirement. This rejection is respectfully traversed.

The comments in the Official Action have been considered, and the claims have been amended to be in full compliance with the written description requirement.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejection Under 35 USC §112, Second Paragraph

Claims 19- 41 have been rejected under 35 USC §112, second paragraph as being indefinite. This rejection is respectfully traversed.

The Official Action asserts that the wording of claim 19 is unclear. However, claim 19 has been amended to clarify the wording.

The Official Action asserts that the claims include trademarks or trade names. However, the claims have been amended to set forth these materials in generic language.

The claims are thus clear, definite and have full antecedent basis.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Rejections Based on QUAKE et al.

Claims 19-25, 31, 33, 34 and 40 have been rejected under 35 USC §102(a, e) as being anticipated by QUAKE et al. (U.S. Publication No. 2002/0025529). Claims 19, 26, 29, 33, 35 and 38 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of URDEA et al. (U.S. Patent 4,910,300). Claims 27, 28, 36 and 37 Claims 19, 26, 29, 33, 35 and 38 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of URDEA et al., and further in view of WELLS et al. (*J. Biol. Chem.*, vol. 261, pages 6564-6570 (1986)). Claims 19, 30, 33 and 39 have been rejected

under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of UEMORI et al. (WO 97/24444) as evidenced by ATKINS (*Physical Chemistry*, 3rd Ed., Freeman and Col., New York 1986, page 278). Claims 19, 32, 33 and 34 have been rejected under 35 USC §103(a) as being unpatentable over QUAKE et al. in view of HYMAN (U.S. Patent 5,516,664).

These rejections are respectfully traversed.

First, it is noted that the instant incorporation of claims overcomes the anticipation rejection.

The present invention pertains to a method for determining the sequence of a nucleic acid molecule. After providing a single-stranded form of the nucleic acid molecule, the primer is hybridized to the single-stranded form to form a template/primer complex. Then the primer is iteratively extended by the addition of a polymerase and a mixture of at least one nucleotide and at least one labeled derivative of the at least one nucleotide.

The important aspects of the present invention include the labeled derivative being formed from fluorophore linked to the nucleotide via a cleavable link formed from a disulfide bond.

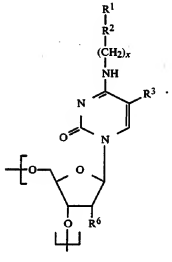
QUAKE et al. pertain to analyzing polynucleotide sequences. Paragraphs 0192 to 0194 of QUAKE et al. discuss the removal of blacking groups and labels via photocleavable or enzymatically cleavable reagents which may or may not have a blocking function. Paragraph 0194 of QUAKE et al. teaches the

use of 3'-5' exonuclease. However QUAKE et al. does not teach the type of nucleotides used in the present invention.

Paragraph 0179 of QUAKE et al. discusses the use of unlabeled nucleotides. However, QUAKE et al. (see, e.g., claim 1) restricts their use to a "microfabricated synthesis channel." Claims 34-40 of QUAKE et al. refer to cyclic incorporation of fluorescently-labeled nucleotides in a mixture where the label is removed by photobleaching.

The Official Action refers to column 8 of URDEA et al., which discusses a polynucleotide probe of the Formula 13:

Formula 13



where R^1 is a reactive group derivatized with a detectable label and R^2 is an optional linking moiety that can be an amide, thioether of disulfide linkage.

In contrast, the independent claims of the present invention set forth the combination of a fluorophore-nucleotide

with a disulphide linker. This can be in the presence of normal, non-labeled nucleotides (see claims 20 and 21). The present invention is not restricted to the use of a "microfabricated synthesis channel."

QUAKE et al. and URDEA et al. also do not disclose an amount of labeled derivative in a nucleotide mixture where the labeled derivative is in a range of 1-50 mole-%.

The other applied art references fail to address the deficiencies of QUAKE et al. and URDEA et al. discussed above.

QUAKE et al. thus fail to anticipate a claimed embodiment of the present invention. One or ordinary skill and creativity would fail to produce a claimed embodiment of the present invention from a knowledge of QUAKE et al. and URDEA et al., and a *prima facie* case of unpatentability has thus not been made.

Further, the present invention displays unexpected results that would rebut any unpatentability that could be alleged. These unexpected results can be observed in the data shown in Figures 5-8 of the present invention, reproduced below.

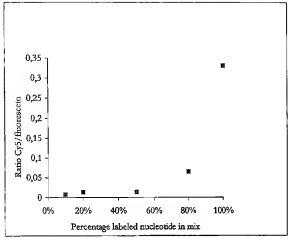


Figure 5.

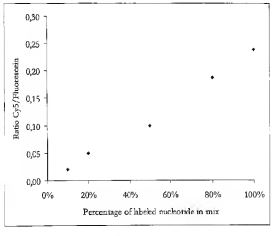


Figure 6

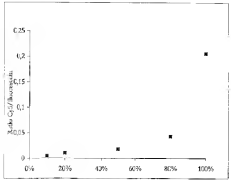


Figure 7.

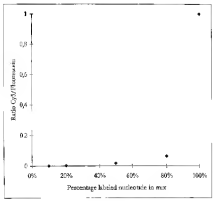


Figure 8

The results in Figures 5-8 show the selectivity of the polymerase for labeled against non-labeled nucleotides. There are clear differences in how the polymerase accepts the different Cy5-SS-nucleotides, in particular between U* and G*. The nodes at the claimed 50% limitation can be clearly observed.

The advantages of the present invention are thus clear.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Conclusion

It is believed that the rejections have been overcome, obviated or rendered moot, and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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